REMARKS

Reconsideration and allowance of the application are respectfully requested in light of the foregoing amended claims and the following remarks.

Applicants acknowledge the modified Restriction Requirement of Groups I-III and that claims 13-28 and 57-59 from previously elected Group I are pending in the application.

Claims 13-28 and 57-59 remain in this application. Claims 1-12, 29-56 and 60-63 have been canceled.

In view of the Examiner's restriction, applicants retains the right to present nonelected claims in divisional applications.

The present application relates to methods of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance.

In particular the present application relates to a method of distinguishing test chemosensitizing compounds which resensitize cancer cells having P-gp/MRP multiple drug resistance from said test chemosensitizing compounds which resensitize cancer cells BCRP or other non-P-gp/non MRP multiple drug resistance to the effects of chemotherapeutic agents.

The chemosensitizing compounds identified by said method do not have the cytotoxic effects of chemotherapeutic agents. In particular, the chemosensitizing compounds identified by said method can resensitize cells to the cytotoxic effects of chemotherapeutic drugs and may be further used in combination with chemotherapeutic agents.

The Examiner has rejected claims 13-14, 17-19, 21, 23-25 and 28 under 35 USC 112 first paragraph, for scope of enablement because the specification, while being enabling for the particular chemotherapeutic agents herein disclosed in the claim, i.e., claims 15 and 26 or the specification (e.g., page 3) and the particular chemosensitizing reversal agents of formula I herein disclosed in the claim, i.e., claims 57-59 or fumitremorgin A, B, C, employed in the claimed methods herein for distinguishing the multiple drug resistance herein, does not reasonably provide enablement for the employment any chemotherapeutic agents and any chemosensitizing reversal agents employed in the claimed methods of the particular treatments herein.....

The Examiner has further rejected claims 13-14, 17-19, 21, 23-25 and 28 wherein the instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation.

In response, applicant respectfully traverse the rejection of claims 13-14, 17-19, 21, 23-25 and 28 because applicants believe the specification is enabling within the meaning of 35 USC

112. Applicants believe that the specification including the testing procedures in the present application enable the invention within the meaning of 35 USC 112 and provide clear guidance.

As presented in the specification on page 4, lines 33-35, and page 14 lines 5-6 "A further feature of the invention is a method of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance which comprises administration of an effective amount of a chemosensitizing reversal agent and a chemotherapeutic agent to which cancer cells are resistant and measuring cancer cell survival."

As presented in the specification on page 5, lines 7-11, "A further aspect of the invention is a method of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance which comprises administration of an effective amount of a chemosensitizing reversal agent and a chemotherapeutic agent to which the cancer cells are multiple drug resistant and measuring chemotherapeutic agent accumulations in the cell."

As presented in the specification on page 5, lines 12-16, "An additional feature of the invention is a method of determining the presence and magnitude of cancer cell BCRP or other non P-gp/non MRP resistance in cancer cells exhibiting such resistance which comprises administration of an effective amount of a chemosensitizing reversal agent and chemotherapeutic agents to resistant cancer cells from humans and measuring cancer cell survival."

Applicants have amended claims 13, and 18 to define the steps in a method of distinguishing P-gp/MRP multiple drug resistance from BCRP or other non-P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance.

Applicants have additionally amended claim 24 to define the steps in a method of determining the presence and magnitude of cancer cell BCRP multiple drug resistance or other non P-gp/non MRP multiple drug resistance in cancer cells exhibiting such resistance.

As an illustration of testing procedures and test results are those described in the specification and in Table 14 on page 33 where the test results of resensitizing S1-M1-3.2 Human Colon Cancer Cells to Mitoxantrone and Toxicity of Fumitremorgin A, B and C and Diketopiperazines against S1-M1-3.2 are presented. The concentration of compounds, Fumitremorgin A, B, C and examples of Formula (I) at the doses described (μM) are toxic doses which kill more than 20% of the cells. When the same compounds are given with Mitoxantrone where the concentration of compound that kills 50% of the cells is less than the toxic doses which identifies these compounds as resensitizing the cells to the chemotherapeutic effects of Mitoxantrone.

To further illustrate the above, the ability of FTC to resensitize S1-M1-3.2 cells to mitoxantrone is shown in Table 7 where cells were incubated for three days with the indicated doses of FTC alone or in combination with 3.2 μM mitoxantrone. Cell survival is estimated using the SRB assay described on page 18 of the specification.

No toxicity of FTC alone was observed in the dose range tested (0.1-80μM). However, in combination with mitoxantrone, 50% of the cells were killed with 0.35 μM of the drug.

In further illustration of the test procedures and results with further chemotherapeutic agents the Examiner's attention is drawn to Table 10, in the specification on pages 27-28, where

multiple antitumor agents are tested with the chemosensitizing compound FTC in multiple cell lines wherein the test data show an increase in reversal activity with mitoxantrone(93 fold), doxorubicin(26 fold) and topotecan(24 fold).

Applicants believe they have provided sufficient working examples.

Applicants have amended claims 14 and 25 which further defined the metes and bounds of the invention as described in Table 6, with a difference score of 22%. Applicants have also, to further define the metes and bounds of the invention as described in Table 2 amended claim 19 with a increase in concentration of the chemotherapeutic agent of 13% or above.

Based on the foregoing, it is respectfully submitted that the present application contains more than sufficient description to enable the skilled artisan to carry out the method set forth in the claims without undue experimentation. Accordingly, withdrawal of the section 112 rejection is respectfully urged.

Additionally, applicants believe that the terms chemotherapeutic agent and chemosensitizing reversal agent are not purely functional distinction. In fact, a chemosensitizing reversal agent is not the same as a chemotherapeutic agent for chemosensitizing agents do not have the chemotherapeutic activity but do resensitize chemotherapeutic agents to multiple drug resistant cancer cells.

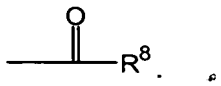
Applicants believe the rejection can be withdrawn in view of the amended claims. Applicant respectfully requests the Examiner to withdraw the Section 112 rejection.

The Examiner has rejected claims 57-59 under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expressions "$R_7NH(CH_2)_v$ or ..." and R_7 is H or ..." and R_8 is selected is from..." .....are not understood since there are no R_7 and R_8 in the formula I..... .

Applicants respectfully traverse the rejection under 35 USC 112 second paragraph.

Applicants point out to the Examiner that within the definition of R_3 in claims 57-59 is the moiety $R_7NH(CH_2)_v$ ..... Further applicants point out to the Examiner that within the definition of R_7 is the moiety



Further R_8 is fully defined within claims 57-59.

Applicants believe that the definitions for R_7 and R_8 are fully described within claims 57-59 and that the rejection under 35 USC 112 as to the indefinite rejection can be removed. Applicant asks the Examiner to remove the 35 USC 112 rejection.

The Examiner has rejected claims 13-15, 17-20, 23-26 and 28 under 35 USC 102(b) as being anticipated by Abe et al. (Br. J. Cancer, 1995, 72, page 418-423, PTO-1449).

Applicants respectfully traverse the 35 USC 102(b) rejection. Abe has two MRP expressing cell lines called T98G and IN500. Abe further uses an MDR-1(Pgp) expressing cell line called CCF-STTG-1 and an additional cell line IN-157 which does not express Pgp or MRP. The IN-157 is not a multiple drug resistant cell line, but is a control for the drug resistant cells. Abe looks for chemosensitizing agents for Pgp and MRP multiple drug resistant cells which is different from the instant invention which is BCRP or other non PgP-nonMRP resistance.

The Abe reference evaluates the ability of various compounds to resensitize drug resistant cells that overexpress MDR-1 or MRP. The instant invention focuses on cell lines which develop resistance by pathways (non-PgP-non-MRP), specifically BCRP. The Abe reference has a different type of resistance which is PgP or MRP multiple drug resistance. In contrast, the instant invention focuses on non-PgP-non MRP resistance.

Based on the foregoing, applicant respectfully requests the Examiner to withdraw the Section 102b rejection.

The Examiner has rejected claims 13-14, 17-19, 23-25 and 28 under 35 USC 102(b) as being anticipated by Tasaki et al. (J. Urology 1995, 154, page 1210-1216, PTO-1449).

The cell line of the Tasaki reference expresses MRP which is not the phenotype in the instant invention, non-PgP(which is the same as MDR-1)-non-MRP.

The Tasaki reference distinguishes between PgP and MRP multiple drug resistance: while the instant invention distinguishes between PgP/MRP multiple drug resistance and non PgP and non MRP multiple drug resistance.

The cell line of the instant invention expresses neither PgP nor MRP multiple drug resistance but expresses BCRP and is therefore distinct from the art.

It is the applicants view that the the Tasaki reference does not inherently distinguish PgP/MRP multiple drug resistance from BCRP or other non-PgP/non MRP because the Tasaki reference only distinguishes between PgP and MRP multiple drug resistance: while the present invention however, distinguishes between PgP/MRP multiple drug resistance and non PgP and non MRP multiple drug resistance.

In addition, it is the applicants view that the Abe reference does not inherently distinguish PgP/MRP multiple drug resistance from BCRP or other non-PgP/non MRP because the Abe reference evaluates the ability of various compounds to resensitize drug resistant cells that overexpress MDR-1 or MRP. The present invention however, focuses on cell lines which develop resistance by pathways (non-PgP-non-MRP), specifically BCRP. The Abe reference has a different type of resistance which is PgP or MRP multiple drug resistance. In contrast, the instant invention focuses on non-PgP-non MRP resistance.

Applicant respectfully requests the Examiner to withdraw the Section 102b rejection.

Finally claims 13-28 and 57-59 are rejected under 35 USC 103 as being unpatentable over Taylor et al. (Br. J. Cancer, 1991, 63, page 923-929, PTO-1449) and Cui et al. (PTO-892). This rejection is also respectfully traversed.

The instant invention is simply not a mixing or combination of two neoplastic agents. What the invention is however, is a method to identify chemosensitizing compounds which resensitize cancer cells which have enhanced resistance to chemotherapeutic agents and in particular to chemotherapeutic agents selected from mitoxantrone, doxorubicin, and topotecan.

Importantly the exemplified test compounds Fumitremorgin A, B and C and the diketopiperazines of Formula (I) are not chemotherapeutic agents at the dose used.

The Taylor et al reference or the Cui et al reference does not solve the problem that is solved by the instant invention.

The Naito et al art does not suggest that it would be desireable to proceed to make the combination of the instant invention.

The Cui et al reference describes the preparation of new diketopiperazine derivatives produced by the fungus Aspergillus fumigatus which includes fumitremorgin C. However, the Cui et al art does not suggest that it would be desireable to proceed to make the combination of the instant invention.

As described by the Examiner, "It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular chemotherapeutic agent such as doxorubicin and mitoxantrone in combination with the particular chemosensitizing reversal agent herein in method of distinguishing P-gP/non MRP multiple drug resistance, and a method of determining the presence and magnitude of cancer cell BCRP or other non-P-fP/non MRP multiple drug resistance in cancer cells exhibiting such resistance."

In response, applicants have not combined compounds taught in the prior art to be useful for the same purpose. Applicants have however, discovered through the method of the invention chemosensitizing compounds which can be combined with chemotherapeutic agents to enhance the ability of the antitumor agents to increase cell death in cells which have drug resistance.

Therefore the instant invention is distinct from the simple combination of two chemotherapeutic agents. Experimental results in Table 2 show that a chemosensitizing agent increases the accumulation of the chemotherapeutic agent in the cell.

The prior art of Taylor et al and Cui et al do not suggest, teach or provide guidance that it would be desirable to combine chemosensitizing compounds and chemotherapeutic compounds as described in the instant invention.

It is the applicants view that Taylor et al and Cui et al neither anticipate nor render obvious the presently claimed invention. Applicant respectfully requests the Examiner to withdraw the Section 103 rejection.

In conclusion, applicants respectfully request that the Examiner enter the amendment, reconsider the rejections in light of the remarks herein, amendments to the claims, and allow the application. Favorable treatment is earnestly solicited.

Respectfully submitted,

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